Author’s response to reviews

Title: Guidelines for the pharmacological acute treatment of major depression: Conflicts with current evidence as demonstrated with the German S3-Guidelines

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Author’s response to reviews:

Response to Editor and Reviewers

We thank the editor and the reviewers for their valuable comments and suggestions. We included them in the revision and hope that the manuscript is now suitable for publication. Below, we pasted the original comments and reply to them pointwise.

Editor Comments:

I advise the authors to take account of the comments of the reviewers and in particular the suggestions to improve the English and to make the article more readable with a more defined structure. In a brief methodological note the authors could explain why they have chosen, after careful scrutiny of the guideline, to address the issues addressed in the following paragraphs.

Reply: We restructured the paper according to the suggestions of Marco Manchetti (editor) and Gabriele Sani (reviewer #2), using the regular structure of a research paper (see changed headlines – introduction, method, results/discussion, conclusion). However, when we tried to put the results and the discussion of the results in separate parts, the manuscript became very hard to read. This is because we do not present a regular study, but a critique of a guideline. So we decided to combine the results and the discussion of the results, as in the original version. Furthermore, the article was submitted as a debate, and according to the journal instructions, the suggested structure is: background, main text, conclusions (https://bmcpsychiatry.biomedcentral.com/submission-guidelines/preparing-your-manuscript/debate). We hope that the structure in the revision is now suitable.

We included a brief methodological note, as suggested by the editor (see Section 2. Methods), and a native speaking psychologist familiar with scientific texts corrected the manuscript.

Reviewer reports:
Antonio Clavenna, Ph.D., M.D. (Reviewer 1): In my opinion, the authors argument in a satisfactory manner that the effectiveness of antidepressants is questionable and that this uncertainty is not fully recognised in the international guidelines concerning the treatment of major depression.

I have a few minor essential revisions to suggest.

Page 4, line 25-30: it seems to me that the sentence "In any case...reported in S3-guidelines" is not very clear.

Reply: this sentence is now changed to: „Therefore, the 25-35% placebo response rate and the approximately 25% difference in response rates between AD and placebo reported in the S3-guidelines substantially deviate from the currently available evidence”

There are a few references cited in the table but not in the text of the manuscript. In my opinion, it should be better to cite them also in the text. E.g. references of meta-analyses reported in table 2 can be cited on page 9, line 57.

Reply: in the revision, we now referenced all studies from the tables in the text (p. 5, second paragraph for references in Table 1; p. 4, first paragraph for references in Table 2)

Reference #41 is an update of ref. #40. I would like to suggest to cite only the latter.

Reply: these are in fact two different publications on the effects of unblinding. One is about trials with binary outcomes [1], one is about gradual (scale) outcome variables [2].

Reference 56 is missed.

Reply: this study was/is referenced in the footnote of Table 2.

Gabriele Sani (Reviewer 2): The Authors made an interesting review on the S3 guidelines and a even larger critics on the guidelines in general. It is surely interesting. However, some point should be addressed in order to make the message stronger and more efficacious.

1) The entire structure of the paper should be revised. It is not easy for the reader to understand how the paper was thought and the general structure of it. I suggest to use a classic structure: Introduction, Methods, Results, Discussion and Conclusion. It would help the reader to better understand the meaning of the paper. I would put all the results found in the results section and all the authors' comments and interpretations in the discussion section.

Reply: see reply to the editor above, who made similar suggestions. We now use the classic structure of empirical papers. However, when we tried to put the results and the discussion of the
results in separate parts, the manuscript became very hard to read. This is because we do not present a regular study, but a critique of a guideline. So we decided to combine the results and the discussion of the results, as in the original version.

Moreover, it would be very important at least to mention that there are alternative treatment for depression, even severe depressions, such as ECT (https://www.ncbi.nlm.nih.gov/pubmed/23212054) or TMS (https://www.ncbi.nlm.nih.gov/pubmed/22827578). Please, see and modify accordingly. Put this consideration in the discussion.

Reply: this is indeed an important point, thank you. However, comparing the risk-benefits of alternative treatments clearly goes beyond the scope of our paper. Furthermore, we made very bad experiences when we included related suggestions in another publication. Unfortunately, the discussion of critics then shiftet away from the main arguments (low efficacy of antidepressants) to problems with alternative therapies.

Thank you for the two citations. However, these studies are about the treatment of treatment-resistant depression, whereas our review of the S3-guideline is about the acute treatment of major depression. Treatment resistant depression is a separate section in the S3-guideline and was not the focus of our review.

To respect the important point Gabriele Sani raised, we included a related statement (Conclusion, second paragraph) and also give an example how different treatments can be compared scientifically, taking into account the risks and benefits. However, we also admitted that an elaboration discussion clearly goes beyond the scope of our paper.

2) English language should be revised.

Reply: the manuscript was corrected by a native speaking psychologist

Additional changes:

Instead of “major depression”, we use “unipolar depression” or simply “depression” to be more in line with the terminology used in the S3-guideline.

We made some simplifications in the text and also removed the perhaps provocative last paragraph where we discussed potential future biases in the guideline development.

In the meantime, an important re-analysis of the Cipriani et al. (2018) meta-analysis was published [3] and we included it in the revision, because this re-analysis is the first that quantified the bias resulting from the placebo-lead-in period.
We made the systematic literature review (retrieved and selected studies) visible via OSF (link is in the manuscript) as well as additional information about our study.

References

